Is the increasing use of evidence-based pharmacotherapy causing the renaissance of complementary medicine?

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This brief commentary considers a possible hitherto infrequently discussed factor that might contribute to the increase in the use of complementary medicines: the difficulties of using placebo within the context of evidence-based medicine, which represents the current standard for pharmacotherapy in most western culture countries. It discusses the possibility of placebo having a similar or better benefit–risk profile compared with an active compound in some diseases, and shows three examples in which this can be concluded from a clinical trial (insomnia, allergic rhinitis, irritable bowel disease). It is proposed that complementary medicine has under these circumstances taken the place of placebo therapy. By this, the commentary does not deny (and does not discuss) the possibility of an effect of complementary medicines other than the placebo effect. However, it recognizes that complementary medicine is open to the therapeutic application of the placebo effect by using a medicine with the claim that it has worked in similar situations and may work in the actual patient, without requiring hard data showing superiority to placebo. Physicians might be more open to the use of complementary medicines for indications in which the placebo effect is high, the conventional therapy carries a risk of side-effects and the omission of treatment with a pharmacologically active compound does not result in irreversible damage. The regulators on their part should probably not require proof of effectiveness compared with placebo in controlled clinical trials. However, whenever used in this sense, the complementary medicine product must unequivocally demonstrate its safety with respect to both the ingredients and the pharmaceutical quality. This is unfortunately not always the case.

Keywords: complementary medicine, evidence-based medicine, placebo, placebo effect, drug development, drug regulation

Whether we look at data on number of publications, research funds, sales figures or the proportion of patients receiving complementary medicine treatment, the trend is obvious. During the last two decades, the interest in and the therapeutic application of complementary medicine remedies has been steadily increasing [1, 2] in practically all countries with a long tradition of rational 'western culture' medicine. This is one of the few facts concerning complementary medicine about which the opponents and protagonists agree. Their views will differ, however, with respect to the causes of this trend. (Complementary medicines are understood in this commentary as homoeopathic and 'similar' remedies which contain only small amounts of pharmacologically active substances. Highly purified herbal products with demonstrated pharmacological effects in man are sometimes also considered as complementary medicines, but not here.)

For a physician whose pharmacotherapy is based on scientific pharmacological principles and evidence from controlled studies, this development is surprising and incomprehensible. In the last decade, we have seen unprecedented achievements in scientific medicine with respect to the treatment of large numbers of hitherto incurable diseases, saving lives and alleviating suffering of many patients. We all agree that these achievements are due to the scientific approach based on experimental evidence and rational principles. We also agree that much more is to be expected in view of the breathtaking speed of the progress of scientific research.

Why then, one would ask, do doctors and patients turn to non-evidence-based pharmacotherapy? Why pursue this path which will very probably never end with

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'hard data' and 'unequivocal results'? Several reasons have been discussed: change of the paradigm as a reaction to the 'blind' belief in science of people in western civilizations; costs; increasing communication with countries and cultures with different approaches to problem solving and medicine; frequent failure of conventional medicine in the management of chronic illnesses; and others.

A possibly important, and after some reflection relatively obvious, reason has, however, found little attention in the medical literature. Let us assume that (i) for some diseases and symptoms placebo therapy has a similar or better benefit–risk profile compared with the use of a pharmacologically active compound, and let us further assume that (ii) in modern western society the use of placebo in the context of rational allopathic therapy is not an option. It follows directly from these two assumptions that complementary medicine represents a valid alternative considering its perception by many patients and physicians as a basically harmless treatment. The main purpose of this communication is to discuss the evidence that the two assumptions hold.

Let us first consider the second assumption concerning the therapeutic use of placebo. In most western countries, an emancipation of the patient to a fully informed partner in therapeutic decisions has been taking place. This development, which is expected to continue due to the increasing information supply and demand in our society, makes a deliberate use of a placebo (i.e. inert compound) in the disguise of an active agent very difficult, if not impossible. I believe that few would disagree about this. At the same time, the increasing promotion of evidence-based pharmacotherapy narrows down the possibilities of using the placebo effect under the disguise of a drug with a low unproven efficacy.

The first assumption: placebo shows a similar or better benefit–risk relationship in some diseases that are treated today with pharmacologically active substances. If we consider on one hand the safety side, there can be no argument about the fact that placebo, being by definition an inert compound, has a definite advantage with respect to the risk of adverse reactions. This is not to say that the therapeutic manoeuvre itself cannot cause the occurrence of adverse effects [3, 4]. There is, however, no risk of adverse effects due to the administered molecule itself as is the case for active compounds. In addition, our society has made important progress with respect to the awareness of the risk associated with drug therapy. Almost every compound which has been proven effective carries some risk of side-effects. Rational evidence-based pharmacotherapy does not exclude the possibility of side-effects, it can only assure the patient that the odds are low compared with the expected benefit. The improvement in the amount and the quality of information that the public and the patients receive leads to an increased awareness of the fact that medicines can harm. But what about the efficacy side? Benefit–risk relationship considerations only make sense in a situation in which the benefit does not equal zero. There is growing evidence indicating that for some diseases and symptoms the efficacy of placebo is not zero. It is well known since Beecher's pioneer work that placebo can represent up to 60% of the total effect of an analgesic agent. Recently, data have been published demonstrating in a direct [5] or indirect [6] way that the placebo effect can even have a measurable substrate in terms of the concentration of endogenous substances known to exert 'pharmacological' effect. Based on this important work, the widespread notion that the placebo effect is due solely to assessment bias and patient or physician imagination can no longer be maintained [7]. We are dealing with a real effect, not an artefact. (For a detailed review of the placebo effect in alternative medicine see a recent review [8] published after this manuscript was submitted for publication.) It is probably sound to assume that in most instances the effect of placebo will be subject to large inter- and intra-individual variations. For life-threatening diseases or diseases with irreparable sequelae it would therefore be imprudent to rely on it. However, there are diseases in which the placebo effect is relatively high, leading to a quite small difference between the efficacy of a pharmacologically active compound and an inert substance. This has resulted in increased costs of the development of active compounds, because large and multiple studies are necessary to prove efficacy (e.g. analgesics, antidepressants, antihistamines). Interestingly, as a result, everybody seems to have accepted the fact that due to the necessity of this extensive testing, the price of the new compounds is high. Nobody, however, has suggested on the basis of the results of these studies that placebo may be, at least as the initial treatment, non-inferior or even superior with respect to the benefit–risk relationship compared with an active compound. We ought to remember that placebo is, in contrast to active substances, devoid of risk of causing adverse effects related to the administered compound and that there is always the possibility of using an active substance after placebo in patients who do not respond to it.

Three examples should illustrate this (several other potential candidates could be found, e.g. common cold, erectile dysfunction, mild to moderate pain). The results presented in Figure 1 were obtained in a well-designed double-blind randomized study comprising 615 patients with insomnia [9]. Table 1 presents data from a double-blind randomized study in 821 patients with seasonal allergic rhinitis [10]. The third example (Figure 2) shows results from a large ($n = 881$) randomized double-blind study in patients with irritable bowel syndrome [11]. It has to be noted that in these studies the placebo effect

is probably underestimated compared with the clinical situation due to a very careful patient selection and a run-in period, which included placebo in the insomnia and allergic rhinitis studies.

Imagine you are a patient suffering from insomnia. The physician will present you with the following choice: 'With drug 1 about half of the patients show an improvement in sleep quality. The effect is, however, somewhat smaller than with drug 2. It also takes longer for a substantial improvement. After 4 weeks, however, the difference between drug 1 and drug 2 is very small.

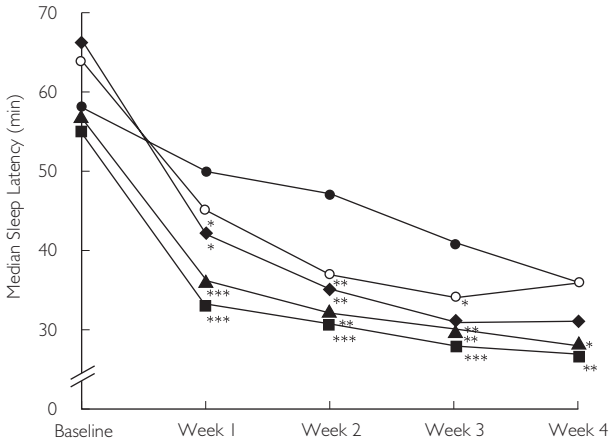

Figure 1 Effect of placebo, zolpidem and zaleplon on sleep latency in a double-blind randomized study in insomnia patients. Reprinted from [7]. Placebo (●); zaleplon, 5 mg (◆); zaleplon, 10 mg (▲); zaleplon, 20 mg (■); and zolpidem, 10 mg (○).

You can always try drug 2 if the improvement with drug 1 is unsatisfactory. Drug 1 has the advantage that no side-effects are known to be caused by this compound. The effect of drug 2 is stronger and more reliable. The side-effects are in general mild and include sleepiness, visual disturbances, and amnesia. These occur in less than 5% of patients. There is a small risk of developing dependence if the drug is used for a longer period of time'. What would be your choice? (It goes without saying that the price of drug 1 is substantially lower.) What would you conclude as a physician with respect to the best treatment for this patient? Cannot we conclude that, based on the available evidence from controlled clinical trials, drug 1 should be the first choice? It shows a similar or better benefit–risk and a better benefit–cost relationship. I accept that one could argue about whether it is too strong a statement that drug 1 should be the treatment of first choice. However, nobody would disagree that some patients, possibly a significant proportion, would prefer to start with a trial of drug 1. Unfortunately (for this particular case; but fortunately, of course, for medical treatment in general), our society and culture with the emancipation of the patient and the widespread dissemination and availability of information precludes the use of the 'optimal' evidence-based treatment. Here, too, western civilization has to pay the price of lost innocence by using 'expensive placebos'. [Another interesting consequence of this development, which is not a topic of this communication but should nonetheless be mentioned in passing, is

Table 1 Twenty-four-hour reflective individual symptom scores (ITT) in a double-blind randomized study in patients with allergic rhinitis. Reprinted from [8].

			Change from baseline treatment (once-daily)		
			Fexotenadine HCl		
Symptom		*Placebo (n = 201)*	*120 mg (n = 211)*	*180 mg (n = 202)*	*Cetirizine 10 mg (n = 207)*
Sneezing	Baseline (mean ± SE)	1.8 ± 0.0	1.8 ± 0.0	1.8 ± 0.0	1.8 ± 0.0
	Change from baseline (mean ± SE)	−0.5 ± 0.0	−0.7 ± 0.0	−0.8 ± 0.1	−0.8 ± 0.0
	Statistical significance⋆		$P = 0.0001$	$P = 0.0001$	$P = 0.0001$
Rhinorrhea	Baseline (mean ± SE)	1.9 ± 0.0	1.9 ± 0.0	2.0 ± 0.0	1.9 ± 0.0
	Change from baseline (mean ± SE)	−0.5 ± 0.10	−0.7 ± 0.0	−0.8 ± 0.0	−0.8 ± 0.0
	Statistical significance⋆		$P = 0.0001$	$P = 0.0001$	$P = 0.0001$
Itchy nose, palate, or throat	Baseline (mean ± SE)	1.9 ± 0.0	1.8 ± 0.0	1.9 ± 0.0	1.9 ± 0.0
	Change from baseline (mean ± SE)	−0.5 ± 0.0	−0.8 ± 0.0	−0.9 ± 0.0	−0.8 ± 0.0
	Statistical significance⋆		$P = 0.0001$	$P = 0.0001$	$P = 0.0001$
Itchy, watery, or red eyes	Baseline (mean ± SE)	1.7 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1
	Change from baseline (mean ± SE)	−0.4 ± 0.0	−0.7 ± 0.0	−0.8 ± 0.0	−0.8 ± 0.0
	Statistical significance⋆		$P = 0.0001$	$P = 0.0001$	$P = 0.0001$
Nasal congestion	Baseline (mean ± SE)	1.8 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	1.8 ± 0.1
	Change from baseline (mean ± SE)	−0.3 ± 0.0	−0.4 ± 0.0	−0.4 ± 0.0	−0.4 ± 0.0
	Statistical significance⋆		$P = 0.0052$	$P = 0.0076$	$P = 0.0199$

⋆ Pairwise comparison of treated group to placebo.

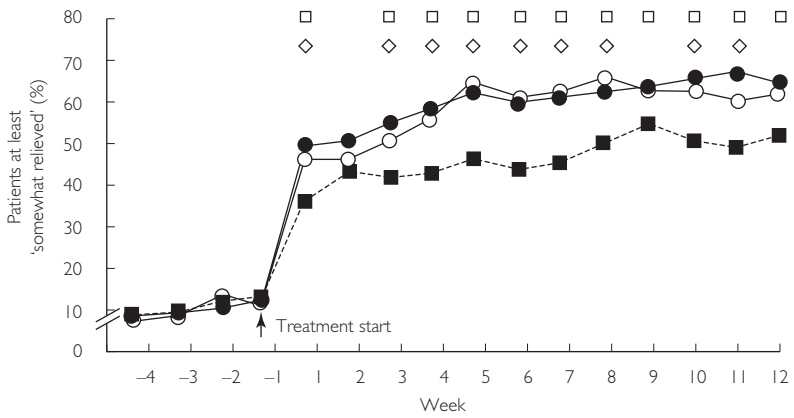

Figure 2 Randomized double-blind study in 881 patients with irritable bowel syndrome. Weekly percentage of patients with a subject's global assessment of relief at least 'somewhat relieved'. Reprinted from [9]. Tegaserod 2 mg b.d. (○); tegaserod 6 mg b.d. (●); placebo (■); $P < 0.05$ (2 mg b.d. vs. placebo) (◇); and $P < 0.05$ (6 mg b.d. vs. placebo) (□).

the problem of 'expensive placebos'. By discrediting the use of medicines for which there is not an unequivocal proof of efficacy compared with placebo, evidence-based medicine facilitates the rise of costs of pharmacotherapy. Costly clinical trials are performed to develop costly new drugs which benefit only a small fraction of patients compared with the use of placebo (or substantially less expensive complementary medicine remedies).]

Based on the evidence presented above, I believe that the exclusion of the therapeutic use of placebo within the context of the conventional evidence-based medicine in western societies should be considered as a possibly important reason for the increasing interest in complementary medicine products. Thus, complementary medicine has in this situation taken the place of placebo therapy. In my opinion, this is by no means a disadvantage of complementary medicine remedies. On the contrary, the scientific community of physicians who are followers of rational and evidence-based pharmacotherapy, of which I consider myself to be a member, should welcome this opportunity of opening a back door for the judicial implementation of placebo in situations for which we have evidence of its positive benefit–risk relation. This means that, with respect to this benefit of complementary medicine products, we are not necessarily interested in new placebo-controlled trials as has interestingly been pointed out, albeit in another context, by the proponents of both complementary [12] and evidence-based medicine [13]. However, whenever used in this sense (i.e. in lieu of placebo therapy), complementary medicine product must unequivocally demonstrate its safety with respect to both the ingredients (and dose) administered and the pharmaceutical quality. This is, unfortunately, not always the case [14].

Before closing I should like to state clearly that this communication by no means denies, explicitly or implicitly, the possibility of an effect of homoeopathic medicines or other complementary medicine remedies other than the placebo effect. This is not the topic of this paper. It implies, however, that complementary medicine (in contrast to rational evidence-based medicine) is open to the therapeutic application of the placebo effect. By this I mean the therapeutic use of a medicine, with the claim that it has worked in some patients and may work in the actual patient, without requiring hard data showing superiority to placebo. And it is here, I believe, where we could learn from our complementary medicine colleagues; not to consider a placebo response merely as a confounding factor interfering with study design but as a therapeutic reality and option, as has been suggested in a recent commentary [7].

In conclusion, I believe that physicians could be more open to the use of complementary medicines for indications in which the placebo effect is high and the conventional therapy carries a risk of side-effects. This, however, only on condition that the safety has unequivocally been demonstrated for the product. The regulators on their part should probably not require proof of the effectiveness in placebo-controlled trials. Instead, and this is probably more important for these therapeutic agents, there should be an adequate labelling, with information about the studies on which the indication is based and, most importantly, a clear demonstration of safety.

Disclaimer

The views of the author are not necessarily the official views of Swissmedic, Swiss Agency for Therapeutic Products.

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